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A Study of Stereocontrol in Spiroketalizations. The Role of Hydroxy-Assisted Chelation.

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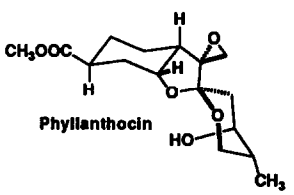
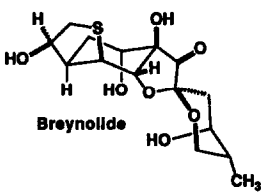
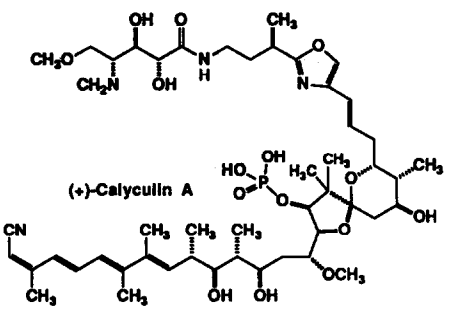
Key Words: spiroketalization; diastereoselection; chelation control

Abstract: *Conditions for kinetic and thermodynamic control in the formation of a series of diastereomeric 1,6-dioxaspiro[5.4]decanes are described. An adjacent hydroxyl substituent directs stereocontrol at the site of spiroketal formation via magnesium cation chelation.*

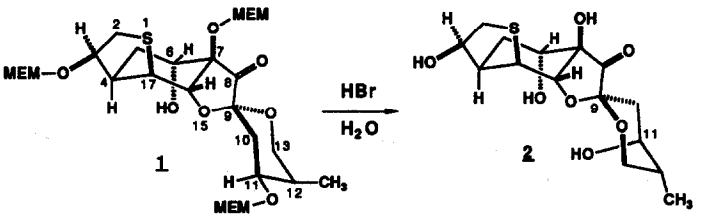
Stimulated by interest in the chemistry of ionophore antibiotics, the synthesis of spiroketals has been a focal point of studies during the last decade.[1] Overall, an analysis of retrosynthetic planning clearly reveals that stereochemical control at the spirocyclic carbon was generally assumed as a result of an acid-catalyzed, thermodynamic equilibration to afford the natural product configuration. In particular, the preparation of 1,6-dioxaspiro[5.4]decanes (5,6-spiroketals) has been prominently studied owing to the presence of this subunit in an array of biologically significant target molecules, such as (+)-phyllanthocin,[2] (+)-breynolide,[3] and recently, (+)-calyculin A.[4] Herein we describe a detailed study of stereoselectivity in the formation of a series of substituted 1,6-dioxaspiro[5.4]decanes. Our data support some surprising conclusions for stereocontrol under kinetic, thermodynamic, and chelation-assisted conditions.







In 1984, in efforts toward (+)-phyllanthocin, we first reported that protic acid-catalyzed spiroketalization of keto triol precursors predominantly afforded diastereoisomers bearing the unnatural configuration of the critical spiro center. It was concluded that this ring-forming process had provided products of a kinetically-controlled reaction. The natural stereochemistry was then obtained via isomerization in the presence of magnesium trifluoroacetate and TFA.[2b, 5] This issue was again confronted in our total synthesis of (+)-breynolide.[3a] In this case, the C_9-*epi*-breynolide 1 was completely isomerized to the natural spirocyclic configuration of 2 in the final deprotection with aqueous HBr. Spiroketal isomerization was anticipated based upon our previous experiences with phyllanthocin derivatives in which many Lewis acids (containing nucleophilic counterions; $MgBr_2$, $SnCl_4$, $TiCl_4$, $ZnBr_2$, etc) promoted the facile deprotection of MEM ethers at C_{11} as illustrated above.[2ab] The 1,3-diaxial relationship of the C_{11}-*hydroxy* and the anomeric oxygen at C_9 provide for powerful Lewis acid chelation and/or hydrogen bonding of this spiroketal diastereomer as the observed thermodynamic product 2.

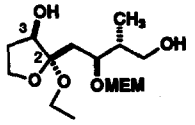
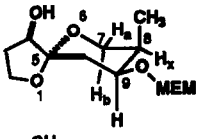
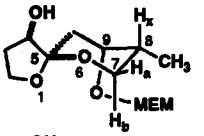
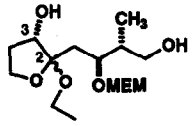
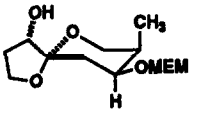
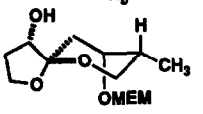
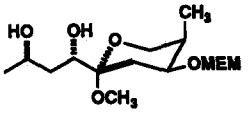
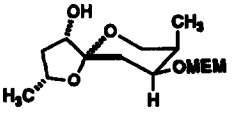
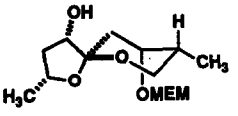
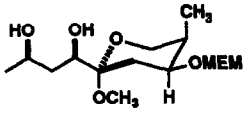
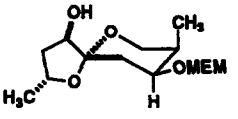
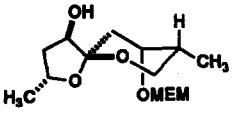
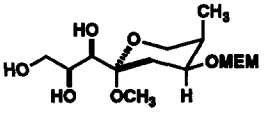
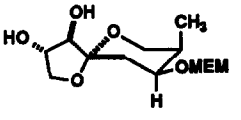
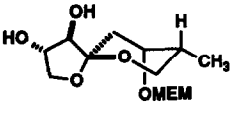
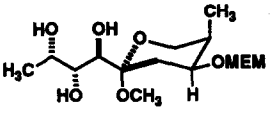
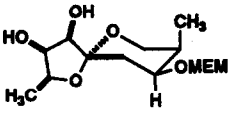
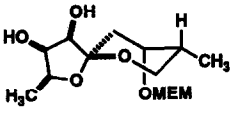
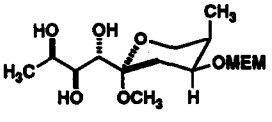
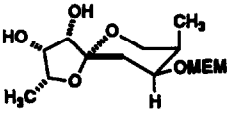
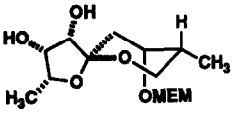


To ascertain the potential for hydroxy-assisted stereocontrol in spiroketalizations, we have examined the ring closure of furanosides and pyranosides as illustrated in Table I.[6] Initially the precursors (Entries 1-7) were cyclized under conditions of kinetic control using pyridinium tosylate (PPTs) in CH_3OH at room temperature. The same ratios were obtained from closures of keto triols (entries 1 and 2). All purified individual spiroketals were resubmitted to these conditions without isomerization. Secondly thermodynamic equilibrations of all individual spiroketals were conducted using excess trifluoroacetic acid (TFA) in CH_2Cl_2 at 0 °C.[7] Ratios of diastereomeric spiroketals were determined for each case (A:B ratios), and were found to be experimentally the same as observed under kinetic control. This suggests the difference in the free energies ($\Delta G^{\ddagger}$) of transition states reflects the difference in energies of the pair of diastereomeric spiroketals. Remarkably, in all examples except entry 7, the major product (A-series) displays the "*unnatural*" spiroketal (C_5) configuration.[8] Stereochemistry of the neighboring C_4- hydroxy has little effect on stereocontrol at C_5 under kinetic or thermodynamic conditions (compare entries 1 and 4 with entries 2 and 3). However, the introduction of magnesium trifluoroacetate (1-3 equivs) under equilibrating conditions affords chelation control in which the cation is tightly bound as a five-membered coordination complex. This provides efficient conversion to spiroketal diastereomers exhibiting a *syn* arrangement of C_4-hydroxy and ketal oxygen (position 6). Overall, the chelation process can enhance ratios of the thermodynamic ketal, or uniquely provide for a "*contra-thermodynamic*" result with high selectivity (entries 1, 4, 5, 6 and 7). Reactions were quenched with saturated, aqueous EDTA solutions to sequester magnesium cation as observed by the dissolution of precipitate.

Stereochemical assignments of our ketals of the A (unnatural) series and B (natural) series were readily recognized by proton coupling constants at C-7, as established via decoupling studies. For example, the A-series displayed geminal coupling ($J_{a\text{-}b}$ = 11 Hz), and two small vicinal coupling constants ($J_{a\text{-}x}$ and $J_{b\text{-}x}$ = 1.5 to 2.5 Hz) for the C_7 methylene. B-series ketals showed two vicinal couplings for $J_{a\text{-}x}$ ~ 6 Hz and $J_{b\text{-}x}$ ~ 11 Hz, in addition to large geminal ($J_{a\text{-}b}$ = 11 Hz) coupling. The assignment of stereochemistry at C_4 was addressed for each case. The B-series spiroketal of entry 5 was unambiguously determined via X-ray crystallographic analysis.[9] Furthermore, *trans*-diols of entry 5 failed to give cyclic derivatives whereas all of the *cis*-diol diastereomers of entries 6 and 7 rapidly formed acetonides (PPTs; 2,2-dimethoxypropane; acetone; 22 °C (95%)). The four isomeric alcohols of entries 3 and 4 were oxidized to a pair of ketones (PCC; CH_2Cl_2; 22 °C), which were stereoselectively reduced with L-Selectride (THF; -78 °C) from the less sterically hindered face the 2,5-*syn*-disubstitution of the tetrahydropyranyl ring. Finally the trifluoroacetates of entries 1 and 2 were assigned by NOE studies,[10] and these conclusions were consistent with our data for entries 3 and 4.

In conclusion, we have defined conditions leading to kinetic and thermodynamic ring closures in the formation of 1,6-dioxaspiro[5.4]decanes. The stereochemical outcome of spiroketalizations may be controlled by neighboring hydroxyl-assisted chelation with magnesium cation under equilibrating conditions. Further efforts toward biologically active ketals are underway.

Table I

Entry	Precursor	Conditions[A] A:B Ratios	Spiroketal Products A- Series	B- Series
1.		K 1.8:1 T 1.8:1 C 1:2.3		
2.		K 1.8:1 T 1.6:1 C 95:5		
3.		K ---- T 2.8:1 C 6:1		
4.		K 1.8:1 T 1.6:1 C 1:10		
5.		K 1.5:1 T 1.6:1 C 1:6		
6.		K 3.3:1 T 3.0:1 C 5:95		
7.		K 1:5 T 1:5 C 95:5		

Conditions[A]: Yields of spiroketals ranged from 72 to 95%. A:B ratios were determined by ^1H NMR integration of the mixture, and subsequent separation of A/B diastereomers.

K = kinetic control: PPTs in methanol at 22 °C for 15-30 min.

T = thermodynamic conditions: TFA (10 to 30 equivs) in methylene chloride at 0 °C for 0.25-1 hr..

C = chelation control: TFA (>10 equivs) in CH_2Cl_2 with $Mg(OCOCF_3)_2$ in Et_2O (1-3 equivs) at 0 ° → 22 °C for 0.5-1 hr; quench with sat. EDTA/H_2O.

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References:

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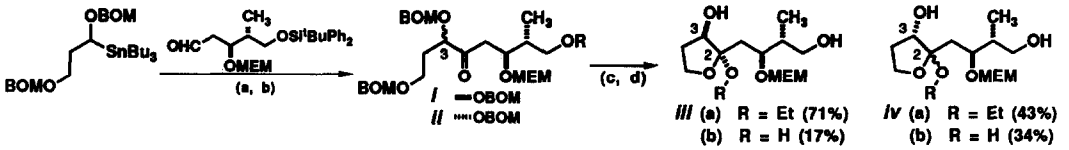
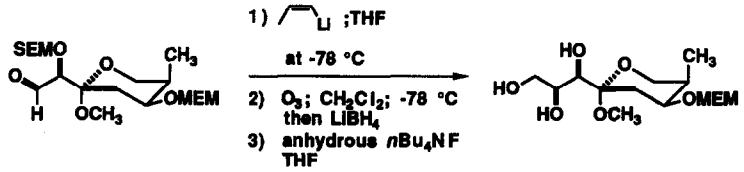
3. For synthesis of (+)-breynolide: (a) Williams, D.R.; Jass, P.A.; Tse, H.-L.A.; Gaston, R.D. *J. Am. Chem. Soc.* **1990**, *112*, 4552. (b) For racemic breynolide: Smith, A.B., III; Empfield, J.R.; Rivero, R.A.; Vaccaro, H.A.; Duan, J.J.-W.; Sulikowski, M.M. *J. Am. Chem. Soc.* **1992**, *114*, 9419.
4. Evans, D.A.; Gage, J.R.; Leighton, J.L. *J. Am. Chem. Soc.* **1992**, *114*, 9434.
5. For a related study: Trost, B.M.; Kondo, Y. *Tetrahedron Lett.* **1991**, *32*, 1613.
6. Our precursors were prepared as illustrated below. The diastereomeric ketones *i/ii* (ratio 1:1) were separated via flash chromatography. Hydrogenolysis of *i* gave a single furanoside *iii*, whereas isomeric *ii* provided a C-2 mixture (3:1 ratio) of ethyl furanosides *iv*. Hemiketals isolated from these reactions were transformed to their respective ketals with triethylorthoformate (cat. PPTs; EtOH; 22 °C; (71-82%)).

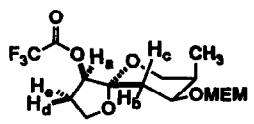


Reagents: (a) *n*BuLi (1 eq.); DME; -80 °C; add aldehyde (68%). (b) $(ClCO)_2$; DMSO; CH_2Cl_2; -78 °C; NEt_3 (90%). (c) Pd-black; H_2 at 1 atm; EtOH-HOAc (4:1). (d) nBu_4NF; THF (85%).
Methyl pyranosides were prepared from the intermediate alcohols *v/vi* (see ref. 3a).

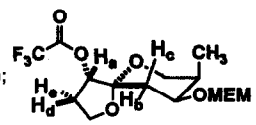
Entries 3 and 4 were available via epoxidation (MCPBA; $CHCl_3$) and hydride reduction (Red-Al; THF; (80)%)). Entries 6 and 7 were produced by oxidation with osmium tetroxide (cat. amt.; N-methyl morpholine-N-oxide; CH_2Cl_2 (90%). Entry 5 was available from our intermediate aldehyde (ref. 3a) as shown below.



7. We have noted that a large excess of acid (TFA) is necessary for facile equilibration. Prolonged reaction times (greater than 1.5 hours) and higher temperatures promoted decomposition. Equilibration was much more difficult to achieve in ethereal solvents.
8. The A-series products may benefit from an unfavorable 1,3-diaxial nonbonded interaction between the C_9 ether oxygen and the ring oxygen at the anomeric C_5 site of the minor isomers. However, deprotection at C_9 leads to facile isomerization and hydrogen bonding in B-series (see also ref. 4).
9. Structural assignment of the B-series diol of entry 5 was unambiguously confirmed by single crystal X-ray diffraction (at -172 °C). All atoms, including hydrogens, were located. Complete crystallographic data are available from the Indiana University Chemistry Library. Request Molecular Structure Center Report 90113.
10. Results of our NOE experiments are summarized below.



Irradiation at H_a (δ 5.26) gave NOE difference enhancements at H_d (0.3%); H_e (1.6%); H_b (0%); H_c (0%).



Irradiation at H_a (δ 4.97) gave NOE difference enhancements at H_b (1.4%); H_c (0.8%); H_d (1.9%); H_e (0.5%).

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